
جمعه سلام

# *Diagnosis of cystic fibrosis*

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- بیماری سیستیک فیروزیس براساس حالتهای فنوتیپی  تی پیک ( بیماری سینوپولونری ، دستگاه گوارش و آنورمالیهای تغذیه ای ، سندرم از دست دهنده نمک یا مرد با آنومالیهای اروژنیتال می تواند مطرح گردد و تائید آن توسط تست عرق صورت می گیرد. این تست در سال 1959 توسط Gibson-Cookeبا تجویز پیلوکارپین توسط Iontophoresis که منجر به تولید عرق می گردد بکار برده شده است. با استفاده از این تست و آنالیز میزان کلر عرق جمع شده می توان تشخیص را مشخص کرد. در کودکان بالای 6 ماه کلرعرق کمتر از 40 mmol در لیتر نرمال در نظر گرفته می شود. و اندازه گیری کلر بیش از 60 میلی مول در لیتر غیرنرمال خواهد بود.

# What is cystic fibrosis (CF)?

A multisystem disease

Autosomal recessive inheritance

Cause: mutations in the cystic fibrosis transmembrane conductance regulator (CFTR)

chromosome 7

codes for a c-AMP regulated chloride channel

# Diagnosis of cystic fibrosis

One or more clinical features of CF

**PLUS**

Two CF mutations

**OR**

Two positive quantative pilocarpine iontophoresis sweat chloride values

**OR**

An abnormal nasal transepithelial potential difference value

# Clinical features of Cystic Fibrosis

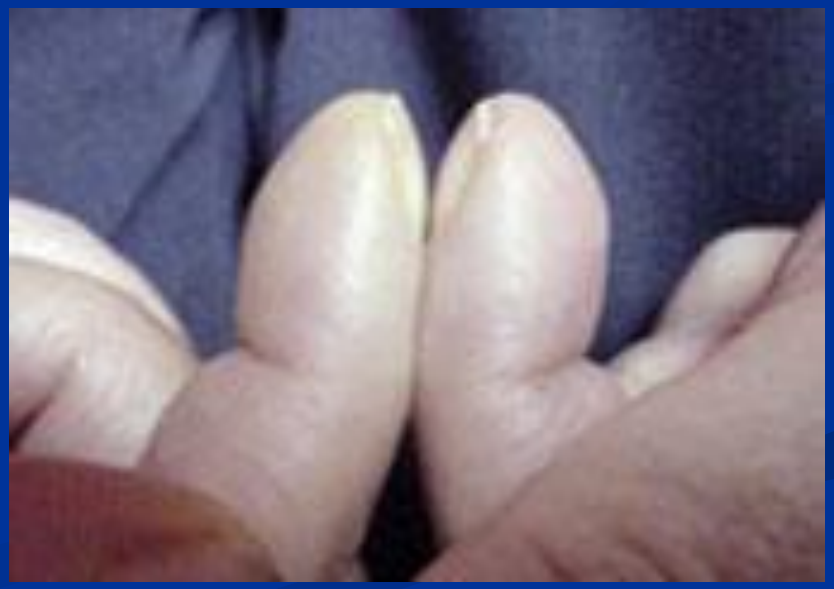
Chronic Sino-Pulmonary Disease

Nutritional deficiency/GI abnormality

Obstructive Azoospermia

Electrolyte abnormality

CF in a first degree relative



Besides the most common mutation, CF chromosomes ΔF508, accounting for about 70% of worldwide, more than 850 mutant alleles have been reported to the CF Genetic Analysis Consortium.

# Types of mutations in CFTR

Class I

Defective protein production

Class II

Defects in processing ΔF508

Class III

CFTR reaches cell surface but regulation is defective (channel not activated)

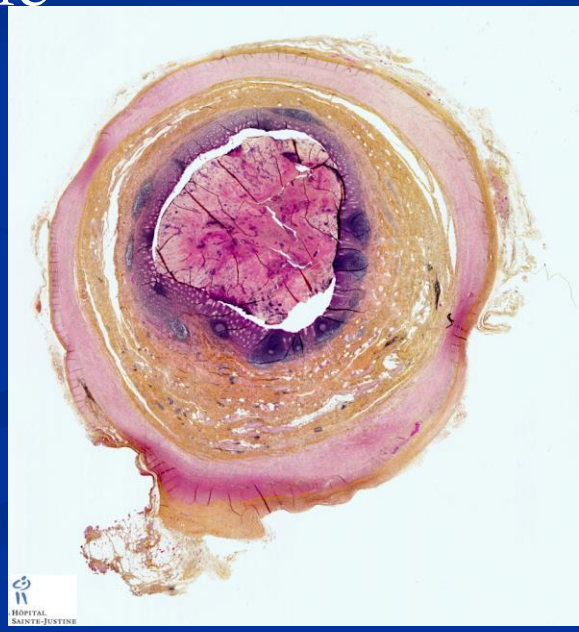
Class IV

CFTR in membrane with defective conduction

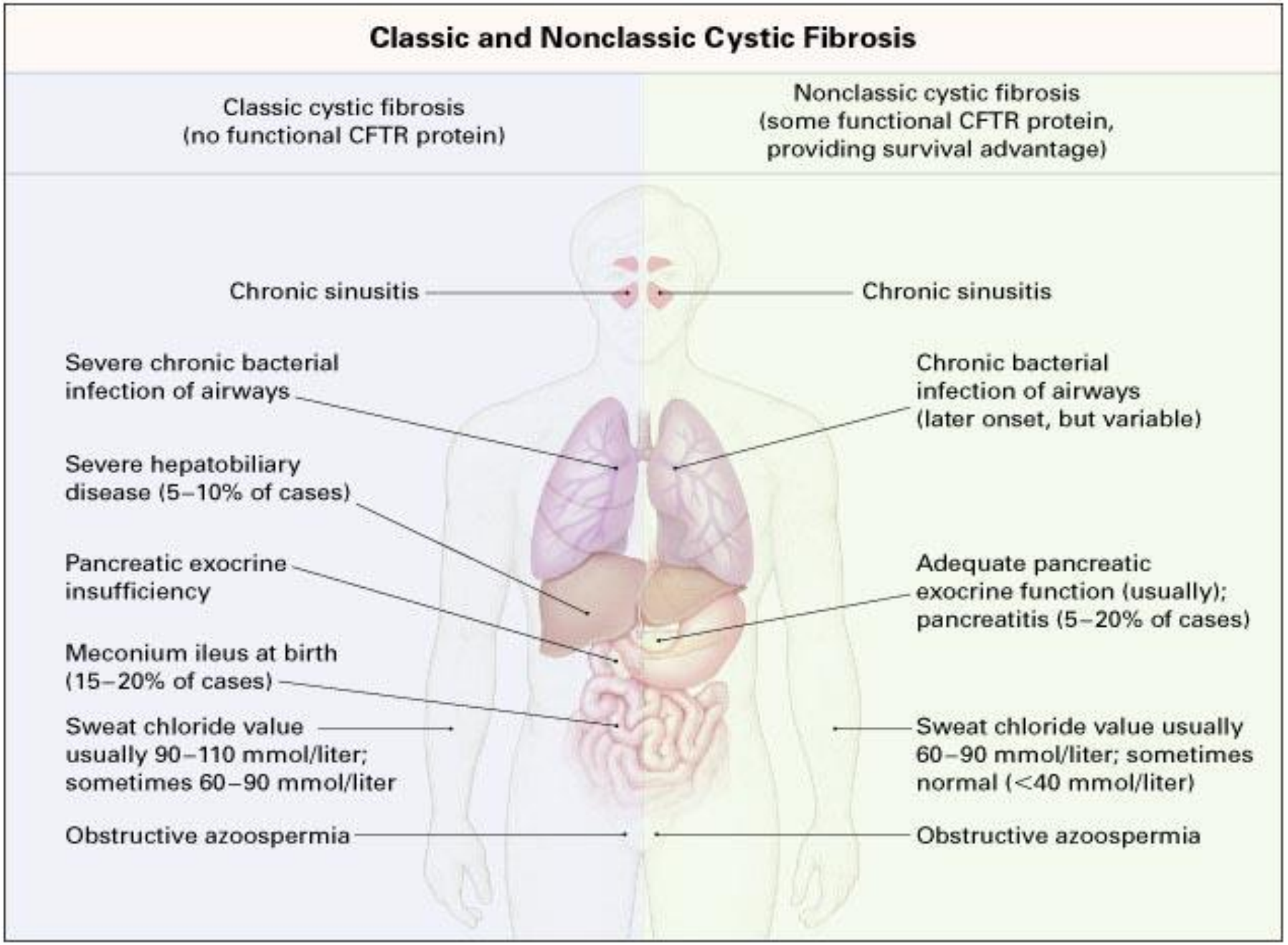
Class V

Decreased synthesis of CFTR

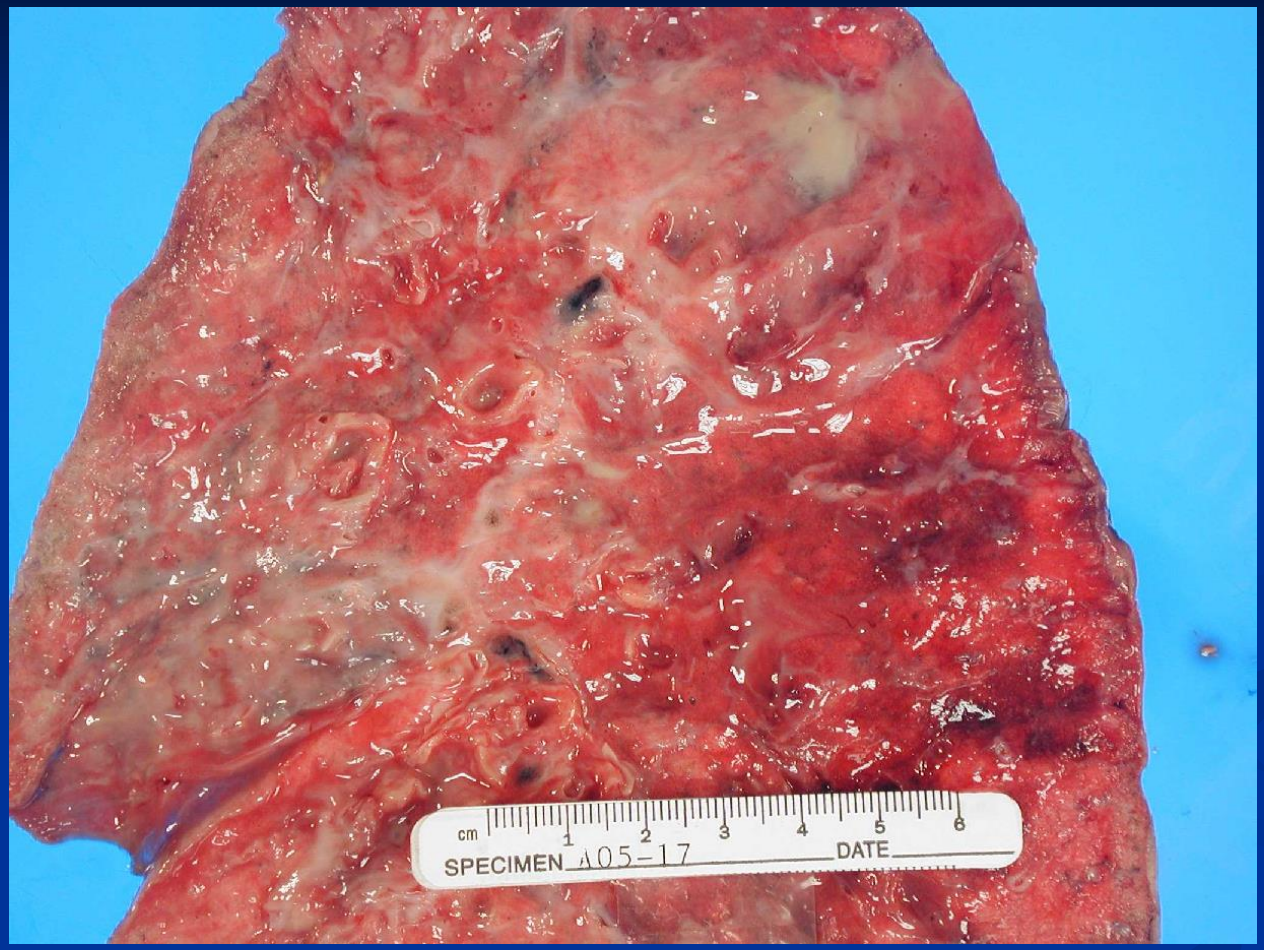
Patients with nonclassic cystic fibrosis have at least one copy of a mutant gene that confers partial function of the CFTR protein, and such patients usually have no overt signs of maldigestion because some pancreatic exocrine function is preserved.



## Classic and Nonclassic Cystic Fibrosis

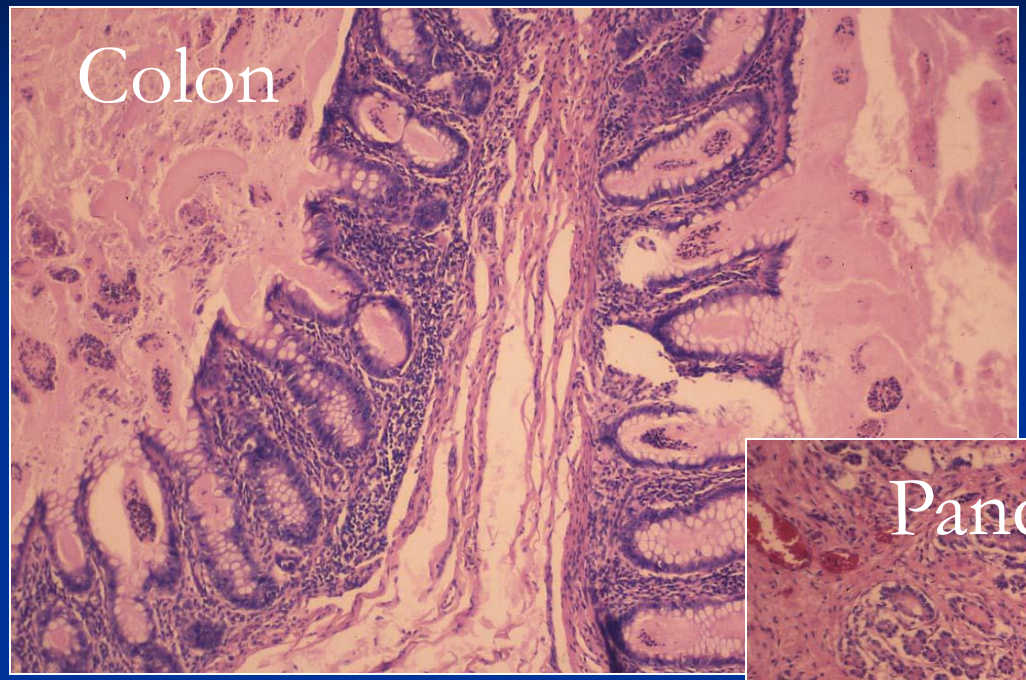


# Presentation of Disease

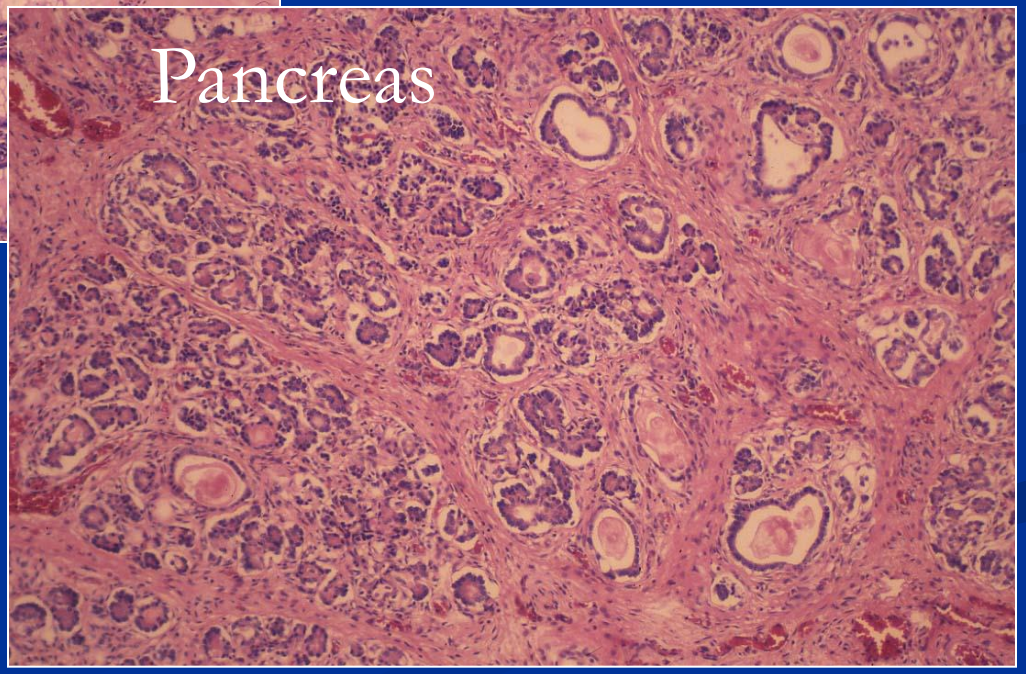



Mucous in the airways cannot be easily cleared from the lungs.

# Presentation of Disease




Sticky mucus secretion




Ducts are filled with sticky mucus. Scaring of tissue.

# Diagnosis

- Typically during 1st year of life
- Presenting symptoms:

• resp. infections • malnutrition • intestinal obstruction

- Early detection: better growth, cognitive functioning, lung functioning
- Sweat Test
- Newborn Screening

# Genotype and Phenotype

The poor correlation between CFTR genotype and severity of lung disease strongly suggests an influence of environmental and secondary genetic factors (CF modifiers).

Several candidate genes related to innate and adaptive immune response have been implicated as pulmonary CF modifiers. In addition, the presence of a genetic CF modifier for meconium ileus has been demonstrated on human chromosome 19q13.2.

Besides patients with atypical CF, there are large numbers of so-called monosymptomatic diseases such as various forms of obstructive azoospermia, idiopathic pancreatitis or disseminated bronchiectasis associated with CFTR mutations uncharacteristic for CF.

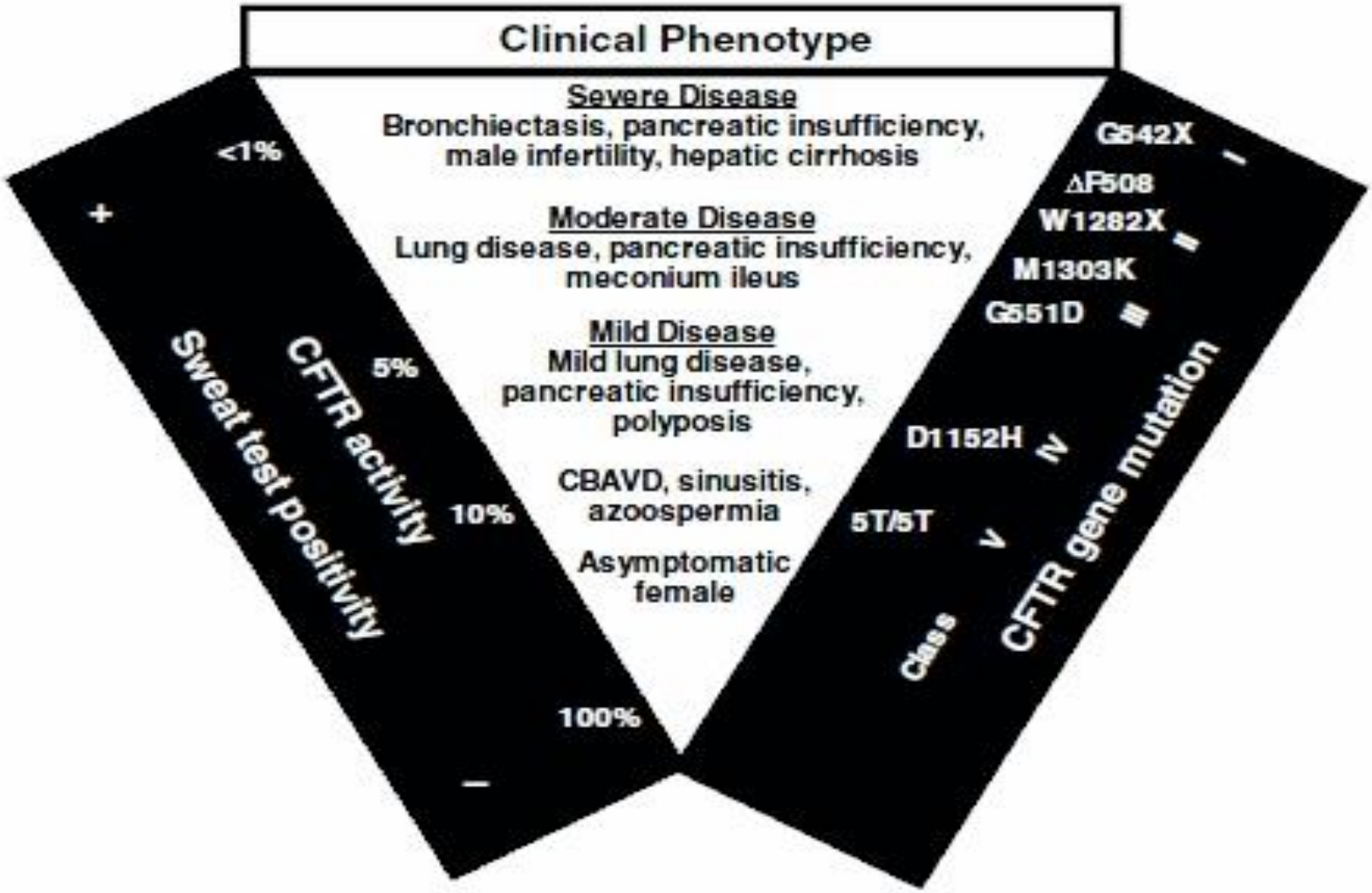



**FIGURE 1.** Severity of cystic fibrosis related to mutation, CFTR activity, and sweat-test positivity (50). Reprinted with permission from Nelson Publishing Inc, Nokomis, FL 34275.

# Diagnostic criteria for cystic fibrosis
# Part 1: Clinical Manifestation of Disease

At least one of the following:

1) **One or more clinical manifestations of CF**

- **Meconium ileus**
- **Chronic bronchitis / bronchiectasis**
- **Chronic infection of the paranasal sinuses**
- **Pancreatic insufficiency**
- **Salt loss syndromes**
- **Male infertility due to congenital bilateral absence of the vas deferens**

2) **Positive newborn screening test**

3) **History of CF in a sibling**

# Diagnostic criteria for cystic fibrosis
## Part 2: Laboratory evidence of CFTR abnormality

**At least one of the following:**

1) Elevated sweat chloride test (98% sensitive)

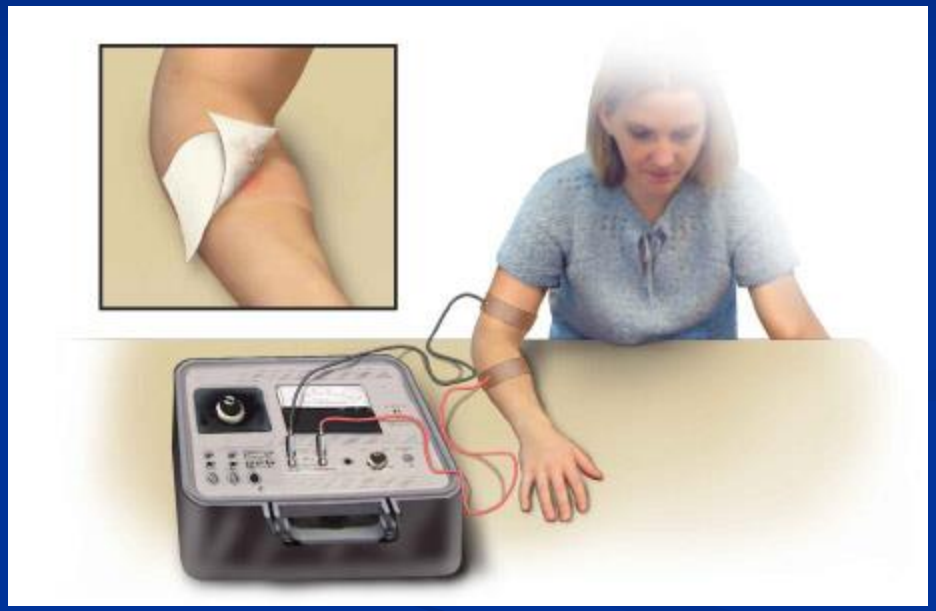
2) Identification of a mutation in each CFTR gene known to cause CF (currently ~81% sensitive)

3) In vivo demonstration of characteristic abnormalities in ion transport across nasal epithelium (not widely available)

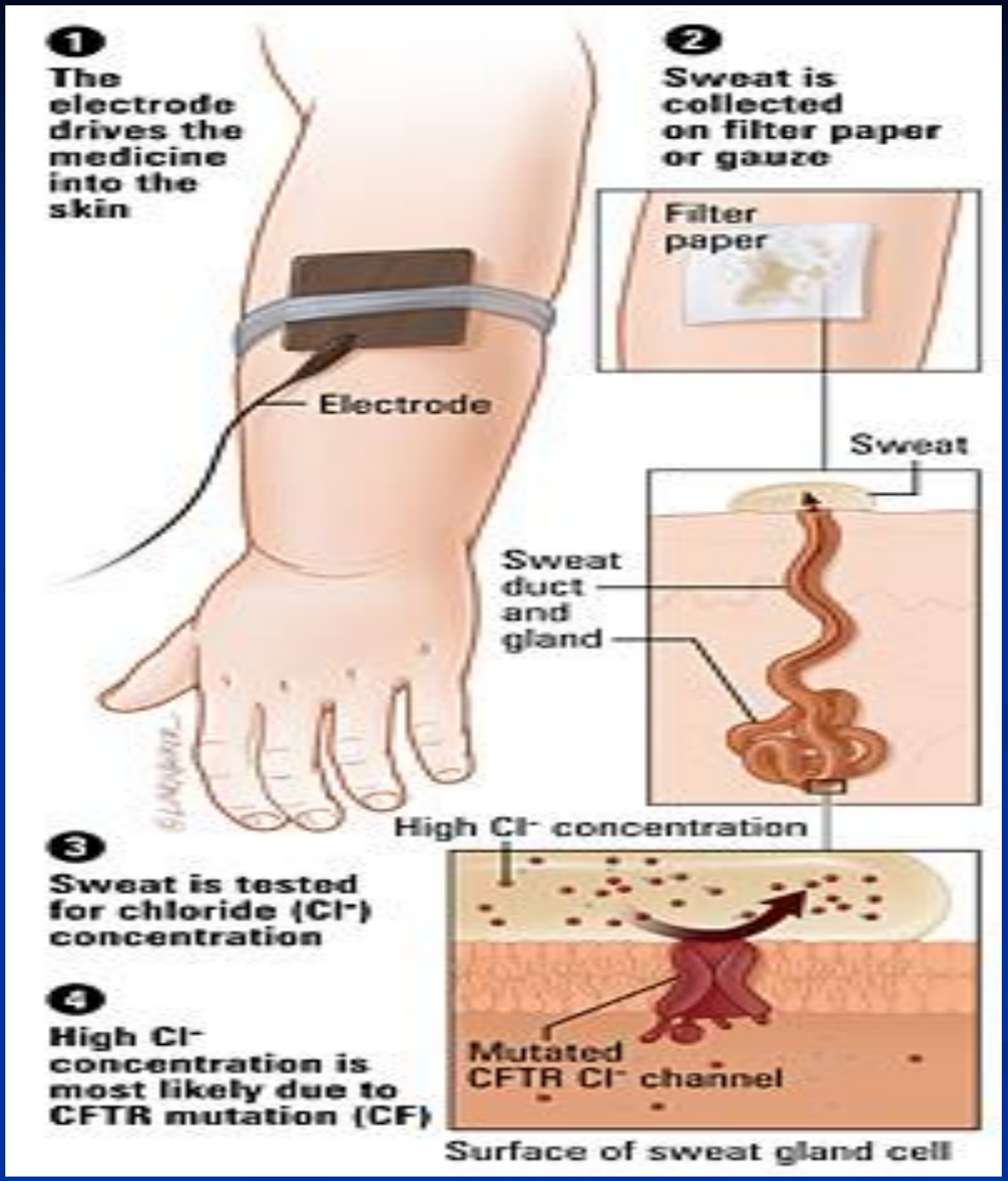
- کلاس I: که توسط نقص سنتز پروتئین مشخص می گردد.
- کلاس III, II: به نقص عملکرد(Processing and Trafficking) ارتباط دارد
- کلاس IV: به عملکرد آنورمال سیستم هدایتی مربوط است
- کلاس V: با نقص mRNA Splicing و کاهش تعداد CFTR با عملکرد نرمال در سطوح آ پیکال همراه است
- کلاس VI : ایجاد پروتئین عملکردی ناپایدار در سطح غشاء آپیکال می نماید.
- بیماری شدید با کلاسهای موتاسیون 1 تا 3 همراه است
- بیماری خفیف: با موتاسیونهای کلاس 4 و 5 گزارش می گردد.
-

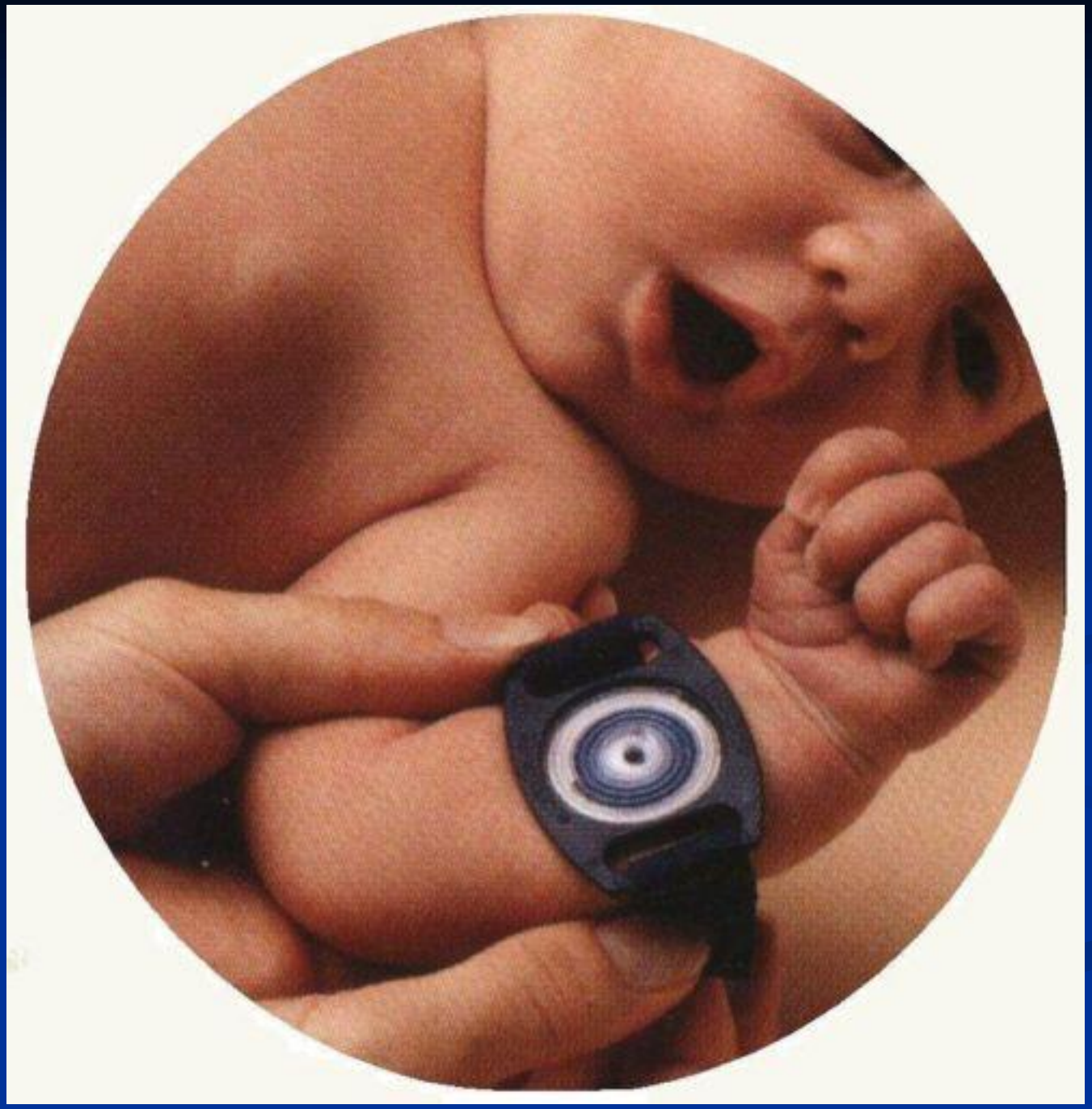
# Diagnosis---Sweat chloride

- Technique first described by Gibson and Cooke in 1950s
- Chemical that stimulates sweating placed under electrode pad; saline under other electrode pad on arm
- Mild electric current is passed between electrodes
- Sweat collected



http://www.nucleusinc.com


1
The electrode drives the medicine into the skin
Electrode
2
Sweat is collected on filter paper or gauze
Filter paper
Sweat
Sweat duct and gland
High Cl⁻ concentration
3
Sweat is tested for chloride (Cl⁻) concentration
4
High Cl⁻ concentration is most likely due to CFTR mutation (CF)
Mutated CFTR Cl⁻ channel
Surface of sweat gland cell



# Sweat chloride

**Positive Sweat chloride:**
**60-165 meq/L**

**Borderine sweat chloride:**
**40-60 meq/L**

**Normal sweat chloride:**
**0-40**

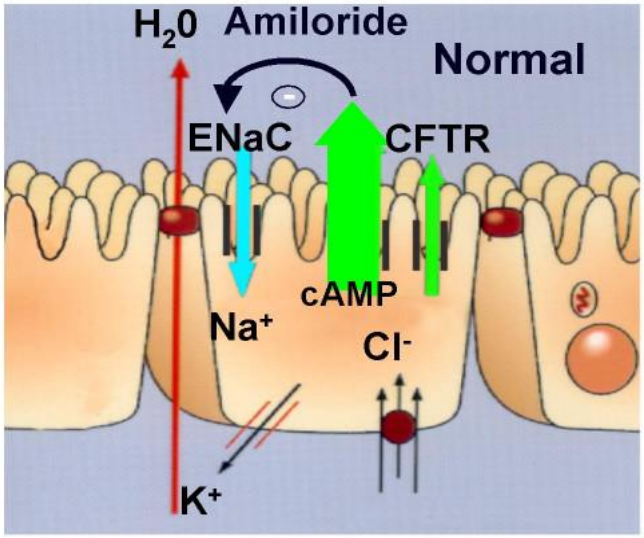
**False positives:**

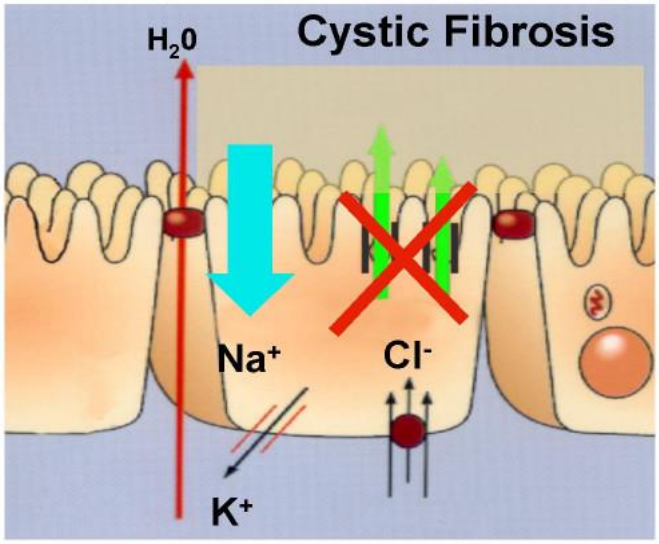
- Hypothyroidism
- Addison disease
- Ectodermal dysplasia
- Glycogen storage disease
- Edema
- Malnutrition
- Lab error (evaporation or contamination of sample)

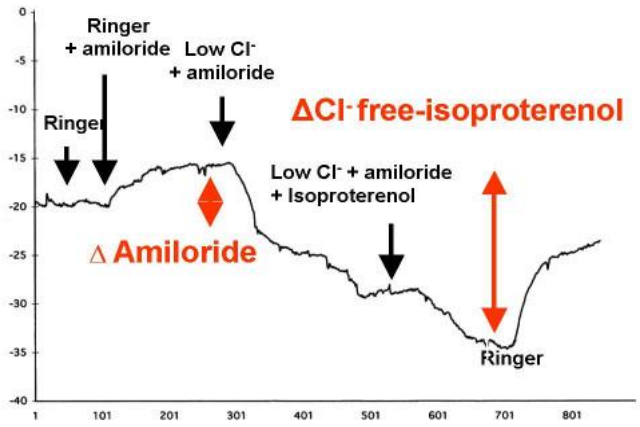
**False negatives:**

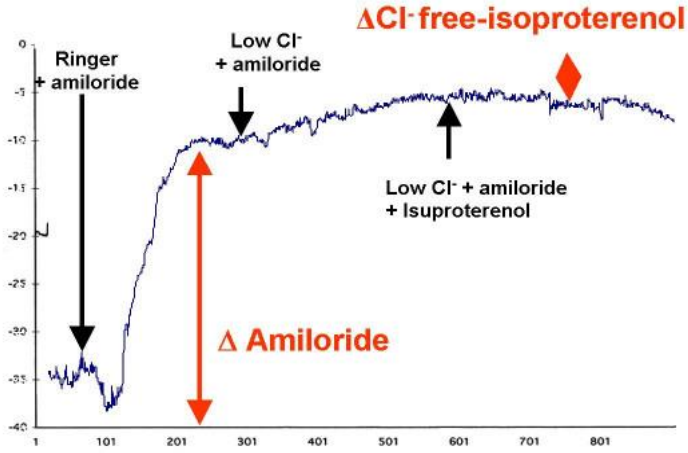
- Edema
- Malnutrition
- Some CF mutations
- Sample diluted

Davis, P. Cystic Fibrosis Since 1938. AJRCCM Articles in Press. Doi: 10.1164/rccm.200505-840OE; 2005.


$H_20$ Amiloride
Normal
ENaC
CFTR
cAMP
$Na^+$
$Cl^-$
$K^+$


$H_20$
Cystic Fibrosis
$Na^+$
$Cl^-$
$K^+$


Ringer
+ amiloride
Low $Cl^-$
+ amiloride
Ringer
$\Delta Cl^-$ free-isoproterenol
Low $Cl^-$ + amiloride
+ Isoproterenol
Δ Amiloride
Ringer
0
-5
-10
-15
-20
-25
-30
-35
-40
1
101
201
301
401
501
601
701
801


$\Delta Cl^-$ free-isoproterenol
Ringer
+ amiloride
Low $Cl^-$
+ amiloride
Low $Cl^-$ + amiloride
+ Isuproterenol
Δ Amiloride
1
101
201
301
401
501
601
701
801

# Prenatal screening

- offering patients option of prenatal screening for CF
- Carrier testing of 23 most common mutations
- Sensitivity of prenatal screening for CF among the white population ≤78%[1]
- lower than that for newborn screening
- sensitivity of prenatal testing in racial and ethnic minority populations is lower[1]

1. Grosse et al. Newborn Screening for Cystic Fibrosis. MMWR.53 (RR13):1-36; 2004.

# Newborn Screening for CF

**Goal: diagnose early---evidence that early diagnosis may be associated with better nutritional outcome and chest radiographic scores[1]**

**Several different protocols in different states**

**Immunoreactive trypsinogen usually first followed by either sweat or DNA testing**

1. Mérelle ME, Nagelkerke AF, Lees CM, Dezateux C. Newborn screening for cystic fibrosis. Cochrane Database of Systematic Reviews. Issue3; 2005.

# Cystic fibrosis related diabetes mellitus

**Screening**

**Oral glucose tolerance test (OGTT)**

**Every two years in patients 10-16 years**

**Any patient with random plasma glucose >180**

**Fasting>=140 mg/dl**

**initiate insulin treatment**

**Fasting<140 and OGTT at 2 hrs>200 mg/dl**

**Home glucose monitoring; consider insulin**

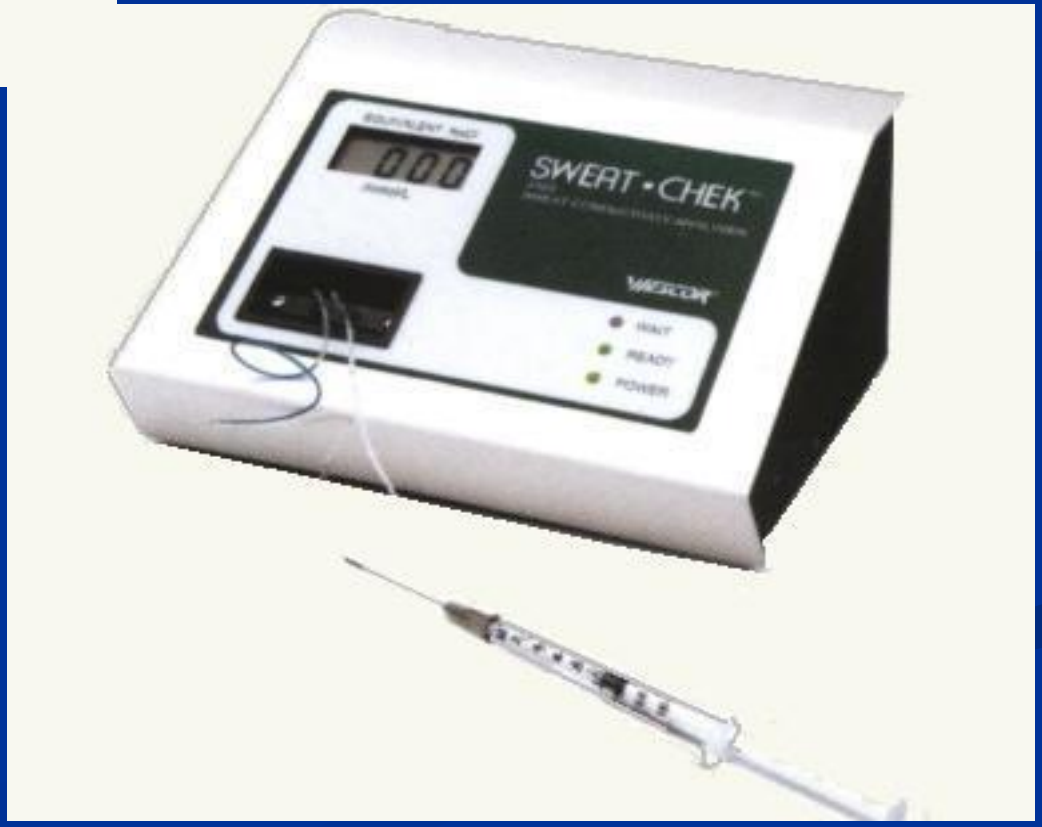
**Fasting <140 and 2 hour 140-200**

**Impaired glucose tolerance**

**OGTT annually**

**Fasting and 2 hour <140**

**Normal glucose tolerance**


SWEAT • CHEK